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Diabetic Nephropathy

0019

Triptolide, an Extracted Phytomedicine Attenuates Glomerularsclerosis in Diabetic Nephropathy Rats via Regulation of Akt/AMPK/mTOR and TGF-beta1/Smad Signaling Activities, Compared with Rapamycin

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Objectives: *Triptolide* (TP), a natural extract from *Tripterygium wilfordii* has been applied extensively for treating glomerularsclerosis (GS) in patients with early diabetic nephropathy (DN) in China. Activation of mTOR plays a critical role in pathologic forms of hypertrophy and proliferation in kidneys under hyperglycemia other than classical TGF-beta1/Smad pathway. Hyperglycemia increases mTOR activity by combined actions of Akt activation and AMPK inhibition. This study aimed to investigate effects and mechanisms of TP on GS, compared with rapamycin through regulating Akt/AMPK/mTOR or TGF-beta1/Smad signaling activities.

Methods: Rats were randomly divided into 4 groups, sham-operated group, TP-treated group, vehicle-given group and rapamycin-treated group, and sacrificed at week 8 after induction of DN by 2 consecutive intraperitoneal injections of streptozotocin (STZ) with an interval of 1 week following nephrectomy. Daily oral administration of TP, rapamycin and saline were started after the second injection of STZ until the sacrifice. Proteinuria, UAlb, BG, biochemical indicators, renal pathological changes, as well as key protein expressions in Akt/AMPK/mTOR and TGF-beta1/Smad pathways in kidneys were examined, respectively. An experiment in glomerular mesangial cells was performed to examine effects of TP on cellular proliferation and collagen synthesis.

Results: Akt/AMPK/mTOR and TGF-beta1/Smad pathways were concurrently activated in kidneys. TP, similar to rapamycin, regulated protein expressions of p-Akt, p-mTOR, p-p70S6K, p-Smad2/3 and TGF-beta1 in kidneys, and ameliorated proteinuria, mesangial matrix expansion, alpha-SMA expression and collagen deposition in glomeruli, without lowering hyperglycemia. Additionally, retardation in glomerularsclerotic development was observed. In HBZY-1 cell line, TP, analogous to rapamycin, decreased high-glucose-induced cell proliferation and expressions of TGF-beta1, p-Smad2/3 and collagen IV.

Conclusion: Activated Akt/AMPK/mTOR and TGF-beta1/Smad pathways jointly contribute to glomerular injury. TP, as a natural regulator, effectively attenuate GS by potential molecular mechanisms involving reduction of mesangial matrix and suppression of Akt and mTOR activation, as well as regulation of TGF-beta1/Smad signaling activity.

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0020

Total Flavone Glycosides of Flos Abelmoschus Manihot Ameliorates Renal Fibrosis in Diabetic Nephropathy Rats via Inhibiting Oxidative Stress and p38MAPK Signaling Activity Compared with Alpha-Lipoic Acid

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Objectives: Total flavone glycosides of *flos abelmoschus manihot* (TFA) has been widely used for treating renal fibrosis in patients with diabetic nephropathy (DN) in China. However, therapeutic mechanisms remain unclear. Oxidative stress (OS) is a determinant during renal fibrotic progress under hyperglycemia. As one of the regulative approaches of OS, p38MAPK signaling pathway plays a pivotal role. This study thereby aimed to investigate effects and mechanisms in vivo of TFA on renal fibrosis, compared with alpha-lipoic acid (ALA) as an antioxidant in clinic, through attenuating OS-related injury and p38MAPK signaling activity.

Methods: Rats were randomly divided into 5 groups, sham-operated group, vehicle-given group, low dose of TFA-treated group, high dose of TFA-treated group and ALA-treated group. TFA, ALA and saline were daily administrated for 8 weeks after induction of DN by streptozotocin (STZ) with unilateral nephrectomy. The DN rats' general state, biochemical indicators, renal pathological changes, OS-related markers, as well as key protein expressions in p38MAPK signaling pathway, fibrogenic cytokines and inflammatory factors were examined, respectively.

Results: DN model rats exhibited typical renal fibrosis, OS-related features and increases in expressions of p-p38MAPK, TGF-β1 and TNF-α. UAlb, BUN, UA, Alb, TG, TC and OS-related markers including MDA, T-SOD, GSH-Px, 8-OHdG and NOX4 in serum or kidneys were ameliorated in treated groups, especially in high dose of TFA-treated group. Of note, TFA synchronously inhibited p38MAPK signaling activity and TGF-β1 and TNF-α protein overexpressions, whereas, ALA only suppressed TNF-α protein overexpression in kidneys.

Conclusion: By means of the DN model rats, we demonstrated that OS promotes renal fibrosis and p38MAPK signaling activity. TFA, as a natural regulator in vivo, can improve OS-related renal damage via regulating protein overexpressions of p-p38MAPK, TGF-β1 and TNF-α, which is different from ALA.

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0023

Deposition of Complement 3 Influences the Prognosis of Nodular Sclerosis of Diabetic Nephropathy

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Objective: To study the influence of the deposition of complement 3 on the prognosis of nodular sclerosis of diabetic nephropathy.

Methods: Clinical and pathological materials were collected from 89 patients who suffered from nodular sclerosis of diabetic nephropathy proved by renal biopsy and took Angiotensin-Converting Enzyme Inhibitors or

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